35 U.S.C. § 112, Second Paragraph

Claims 76, 77, 82 and 83 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. The claims are alleged to be ambiguous because the claims are unclear as to what final form the primer is in, a tagged primer hybridized to a template or an extended tagged primer which is either being hybridized to (claim 76 and 82), or separated from, the template (claims 77 and 83).

Applicants respectfully traverse. The claims encompass various embodiments of the primer which the Office has correctly paraphrased. Claim 76 and its dependents are directed to a primer which is hybridized to a template and extended by a polymerase. Claim 82 and its dependents are directed to a set of primers, wherein each primer of the set has been hybridized to a template and extended by a polymerase. However, without conceding the correctness of the Office's position and to advance prosecution of the application, claims 76, 77, 82 and 83 have been amended. In view of these amendments, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 105 to 107 also stand rejected under 35 U.S.C. § 112, second paragraph on the ground that while they depend from claim 101, which depends from claim 75, which is drawn to a tagged primer base-paired to a template, they also recite a further method in which the primer is extended and is separated from the template. Claims 109 to 111 also stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The claims are alleged to be ambiguous because while they are drawn to a tagged primer, they are also recited to a further method comprising a chain termination DNA sequencing reaction.

Without conceding the correctness of the Office's position and merely to advance prosecution of the subject application, claims 105 to 107 and 109 to 111 have been amended herein. In view of these amendments, reconsideration and withdrawal of these rejections are respectfully requested.

35 U.S.C. § 102(b)

Claims 73–75, 84–86, 89, 90, 101, 102 and 104 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Draper et al. Draper et al. is alleged to teach a poly(C)sequence which is attached with a fluorescent label through an amine linker. Although not explicitly disclosed that the sequence is a primer and that it can be extended by a polymerase, it is alleged to be inherent that the sequence is also a primer. Draper et al. also is alleged to disclose the primer hybridized to a template in that Draper et al. shows the interaction between the fluorescently tagged poly (C) and rRNA of the 30S ribosomal units.

Applicants respectfully traverse. Draper et al. does not teach a primer as defined herein and therefore, also does not teach a primer hybridized to a template. The primers of the subject invention are comparably smaller than the polynucleotides of Draper et al. The claims have been amended to more clearly point out and distinctly claim that tagged oligonucleotides and their extension products, rather than polynucleotides, are the subject of this invention. Thus, the polynucleotides of Draper et al. are much larger than the oligonucleotide primers of the subject invention.

Furthermore, the polynucleotides of Draper et al. are not always capable of forming stable duplexes with the template. In order to serve as a primer, a poly- or oligonucleotide must be able to base-pair with its template, particularly in the region of the 3' end of the primer. Draper et al. states that fluorescent labeling by his method "weakens the polynucleotide binding [to ribosomes] ...." (lines 10-11 of Abstract). On page 1775, second column, at the third and fourth lines up from the bottom of the page, it is stated that "... a small amount of degradation occurs during these [labeling] procedures ...." Although perhaps not an issue for the analysis of longer polynucleotides, degradation of short oligonucleotides, such as are the subject matter of the claims herein, would almost certainly have adverse effects on both specificity and efficiency of hybridization.

The paragraph bridging pages 1777 and 1778 discusses the effects on base-pairing properties of substitutions similar to those described by Draper et al. It is stated that such substitutions weaken the C-G base pair (last four lines on page 1777). Later in the same

paragraph, it is further stated that destabilization of base-pairing is a likely result of the modifications described by Draper et al. (page 1778, first column, last three lines of first partial paragraph). Again, even though it is stated that these are likely to be small effects, they will have much more severe consequences for the hybridization ability of a short oligonucleotide, such as is commonly used for priming.

On page 1778, second column, last sentence of the first partial paragraph, Draper et al. again mentions that their labeling technique will affect the base-pairing properties of nucleotides so labeled: "Further studies are in progress to determine the amount by which the NBF label affects base pairing."

Draper et al. presents data concerned with the binding of labeled polynucleotides to ribosomes or ribosomal subunits. However, Draper et al. provides no direct evidence that this binding is due to base-pairing. Indeed, from the data presented, the binding is likely mediated by the S1 ribosomal protein. See page 1780 at the paragraph bridging the first and second columns: "... S1 provides the environment responsible for altering the NBF fluorescence." (Alteration of NBF fluorescence is a measure of ribosome binding to the NBF-labeled polynucleotide, see, e.g., page 1778, second column, second full paragraph.)

Thus, from the teaching of Draper et al., the use of his method to label an oligonucleotide used for priming would be likely to generate a fragmented product with weakened base-pairing ability. Accordingly, Draper et al. cannot anticipate the claims. See Glaxo Inc. v. Novopharm Ltd., 34 USPQ2d 1565, 1567 (Fed. Cir.), cert. denied, 116 S.Ct. 516 (1995) (anticipation claim rejected on ground that process disclosed in prior patent did not always produce the compound of the patent in suit).

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

35 U.S.C. § 103

Claims 76–83, 87, 88, 91–100, 103 and 105–111 stand rejected as allegedly anticipated over Draper et al. in view of Sanger et al. Draper et al. is cited for the teachings noted above and Sanger et al. is cited for teaching chain extension of a radioactive primer from a template to produce products which are subjected to nucleotide sequence analysis. It is the Office's position that it would have been *prima facie* obvious to prepare a fluorescently tagged primer which is hybridized to a template and extended by a polymerase and preparing the resulting products as those drawn in the claims.

Applicants respectfully traverse and incorporate by reference their remarks concerning Draper et al. as outlined above. Because Draper et al. does not teach or suggest the primers claimed herein, its combination with Sanger et al. cannot render the rejected claims obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

Obviousness-Type Double Patenting

Claims 73, 74, 78–80, 84–87 and 89–91 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 4 and 7 of U.S. Patent No. 5,118,802. Applicants respectfully defer responding to this rejection until allowable subject matter has been indicated in this application.

III. CONCLUSION

Applicants respectfully request reconsideration in light of the proposed amendments and remarks set forth above.

Enclosed with this response is a check in the amount of $566.00 in payment of the fee for the two month extension of time and eight additional claims. In the event the Assistant Commissioner determines that additional fees are required, Applicants authorize the Assistant Commissioner to charge any additional fee required for this submission to Deposit Account No.

03-1952 (**Reference No. 24313-20001.05**). However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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